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Commentary

Comment on 'Long noncoding RNA UCA1 promotes glutamine-driven anaplerosis of bladder cancer by interacting with hnRNP I/L to upregulate GPT2 expression' by Chen et al.'"

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ABSTRACT

Bladder cancer is prevalent cancer worldwide with poor outcomes for patients with high-grade disease. Emerging evidence shows that alteration of metabolic status drives tumorigenesis in bladder cancer. As long noncoding RNA urothelial cancer associated 1 (UCA1) is known to play an essential role in cancer metabolisms, such as glycolysis and glutaminolysis. Chen et al. report the novel function of UCA1 in glutamine metabolism through interacting with heterogeneous nuclear ribonucleoproteins (hnRNPs) I and L (hnRNP I/L). This study reveals that UCA1 promotes glutamic pyruvate transaminase 2 (GPT2) expression at the transcription level in mechanistic studies. Inhibition of either UCA1, hnRNPI/L, or GPT2 significantly reduces bladder cancer tumor growth in the mice model. This work explores a new mechanism for glutamine metabolism and the novel therapeutic target of the UCA1-hnRNPI/L-GPT2 axis across malignancies.

Bladder cancer is one of the most globally distributed malignity diseases, with over 0.5 million new cases reported in a year and 0.2 million deaths [1]. The classifications of bladder cancer are non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) [2]. NMIBC composes 80% of diagnosed bladder cancer and is identified to carry mutations in fibroblast growth factor receptor 3 (FGFR3), tumor suppressor TP53, and DNA helicase ERCC2 [2]. MIBC comprises 20% of diagnosed bladder cancer and is known to harbor mutations in FGFR3, tumor suppressor TP53, transcriptional activator ELF3, tumor suppressor RB1, Histone demethylase KDM6A, and DNA helicase ERCC2 [2]. While NMIBC is often identified locally in the urothelium (stage Ta) or the lamina propria (stage T1), MIBC is more malignant with its invasion to the muscle (stage T2) or beyond (stages T3 and T4) [1,2]. In addition to surgery, patients with bladder cancer usually receive radiotherapy alone chemotherapy, such as adriamycin, mitomycin C, epirubicin, thiotepa, gemcitabine, platinum-based agents, and doxorubicin. However, the outcome of these treatments remains poor [1,2].

Metabolic reprogramming has substantially emerged as a cancer progression and treatment hallmark in bladder cancer [3]. An association of metabolic reprogramming with tumor proliferation, metastasis, and drug responses is revealed as changes in metabolic processes, such as aerobic glycolysis, TCA cycle, glutamine catabolism, macromolecular synthesis, and redox homeostasis [4]. Several metabolites are a critical part of a wide variety of tumorigenesis [5]. Among them, glutamine, the most abundant amino acid in the body, is one of the essential substances as glutamine-related metabolic adjustment results in enhanced glutaminolysis, an addict to glutamine, and glutamine anaplerosis various cancer types [5], including bladder cancer [6]. Writing in the *Translational Oncology*, Chen et al. report a study of glutamine-driven anaplerosis regulated by the interaction of long noncoding RNA urothelial cancer associated 1 (UCA1) and heterogeneous nuclear ribonucleoproteins (hnRNPs) I and L (hnRNP I/L) through activating glutamic pyruvate transaminase 2 (GPT2) transcriptionally in bladder cancer *in vitro* and *in vivo* [7]. This study is an excellent example of how combining data mining and typic biology platforms *in vitro* and *in vivo* can drive translational research on long non-coding RNAs (lncRNAs) in dysregulated cancer metabolism in bladder cancer. As previous studies have shown that UCA1 stimulates glutaminolysis through targeting miR-16 [8], this study further found that by interacting with hnRNP I/L, UCA1 drives glutaminolysis through enhancing glutaminolytic enzymes GLS2 and GPT2 [7]. This work suggests that UCA1 may play a potential role translationally and clinically for bladder cancer via the regulation of cancer metabolism [7].

UCA1, an oncogenic non-coding RNA, functions in cancer cell growth, invasion, migration, metastasis, and angiogenesis [9].

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Overexpression of UCA1 is associated with wide e-spectrum of cancer types, including bladder cancer [7,9]. UCA1 expression can be upregulated by Ets-2, C/EBPα, TAZ/YAP/TEAD, and HIF1-α in responses to hypoxia conditions [9]. On the contrary, CAPERα/TBX3 and miR-1 are negative regulators for UCA1 expression [9]. UCA1 mediates proliferation, chemoresistance, apoptosis, metastasis, and metabolism in tumorigenesis. For example, UCA1 promotes bladder cancer proliferation by interrupting the interaction between BRG1 and p21 [9]. For the role in cancer metabolism, UCA1 drives aerobic glycolysis by regulating mTOR-STAT3- hexokinase 2(HK2) signaling [9]. While UCA1 has to be reported to promote glutamine metabolism by targeting miR-16 in bladder cancer versatile in cancer progression [8], this study provides another mechanism for UCA1 regulating glutamine metabolism through the UCA1-hnRNPI/L-GPT2 axis. Inhibitory of glutamine metabolism has been proposed and is under development for anticancer treatments. Such as inhibitors of isocitrate dehydrogenase 1 (IDH1), glutaminase (GLS), glutamate dehydrogenase (GLDH), or other vital enzymes could be used in combination with standard chemotherapy treatments [5]. As Chen *et al.* discussed, using aminooxyacetate (AOA, aminotransferase inhibitor) blocks the conversion of glutamate to α-KG could be applied in the treatment of bladder cancer. On the other hand, glutamine analogs (DON, acivicin, and azaserine) and SLC1A5 inhibitors (GPNA and V-9302) can be examined for their therapeutic effects on bladder cancer with UCA1-mediated glutamine reprogramming [10]. It has been proof-of-concept that utilizing gene therapy to block UCA1 using CRISPR represses bladder cancer malignancy [11]. While more CRISPR clinical trials are undergoing an emerging promise against deadly diseases [12], targeting UCA1 using CRISPR technology would be a promising strategy for cnacer treatments in the future.

In conclusion, the remarkable study by Chen *et al.* provides new knowledge of how the UCA1-hnRNPI/L-GPT2 axis regulates glutamine metabolism in bladder cancer. The authors' findings also reveal a potential anticancer strategy. It's exciting to learn the authors conducted a mice model to study the roles of UCA1, hnRNP I, RNP/L, and GPT2 in bladder cancer growth tumors. The crosstalk between cancer metabolism, tumor microenvironment, and cancer immunity through the UCA1-hnRNPI/L-GPT2 axis should be further elucidated. Given the CRISPR technology is not applied in this study, the authors indeed have demonstrated a solid translational study with the approaches of molecular biology, database analysis, and animal models.

Financial and competing interests' disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

CRediT authorship contribution statement

Chi-Wei Chen: Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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